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Countercurrent system

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The production of concentrated urine is achieved by osmotic equilibration of the collecting duct luminal fluid with the hypertonic medullary interstitium. The principals of countercurrent multiplication, originally proposed by Kuhn and Ryffel in 1942 [1] are now generally accepted as the mechanism by which a hypertonic medulla is created. Several studies during the 1950's established that osmolality increases from the cortex to the papillary tip in the loops of Henle, collecting ducts, and vasa recta [2–4]. Micropuncture studies during the 1960's supported the hypothesis that the single effect for countercurrent multiplication was located in the ascending limb of the loop of Henle [5, 6]. The single effect in the outer medulla, active NaCl absorption by the thick ascending limb (TAL), was established by isolated perfused tubule studies [7, 8]. The single effect in the inner medulla was less clear. Direct measurement failed to demonstrate active NaCl absorption in the thin ascending limb [5, 9]. In 1972, two studies proposed a mechanism by which countercurrent multiplication could occur in the inner medulla without active transport [10, 11]. In this review, we will discuss the "passive" mechanism and the tubular transport properties upon which this model is based, discuss recent data on urea transport and its implication for the countercurrent mechanism, and discuss potential sources of controversy and unresolved questions concerning the countercurrent system.

The passive mechanism

In 1972, Stephenson [11] and Kokko and Rector [10] simultaneously proposed a multisolute model in which the osmolality of the fluid in the thin ascending limb was reduced without active transport. This model, illustrated in Figure 1, utilizes the potential energy of the chemical gradients for urea and NaCl established by the unique transport properties of inner medullary nephron segments (discussed below) to perform osmotic work, that is, to dilute the fluid in the thin ascending limb. According to the model, fluid in the thick ascending limb is diluted by active NaCl absorption. The reabsorbed NaCl, along with the urea which is absorbed from the inner medullary collecting duct, generate a hypertonic medullary interstitium, which in turn concentrates NaCl within the thin descending limb by water abstraction. In addition, if vasopressin is present, water is absorbed from the cortical and outer medullary collecting duct while concentrating urea within the collecting duct lumen. This urea is absorbed from the inner medullary collecting duct, generating a very high urea concentration within the inner medullary interstitium. The fluid which enters the thin ascending limb has a higher NaCl concentration and a lower urea concentration than the interstitium, resulting in passive NaCl absorption and dilution of the thin ascending limb. Thus, energy expended in the thick ascending limb is coupled to passive NaCl absorption in the thin ascending limb [10, 11].

This model depends upon the following assumptions: (1) the thin descending limb is highly permeable to water but impermeable to NaCl and urea; (2) the thin ascending limb is impermeable to water, highly permeable to NaCl, and somewhat permeable to urea; (3) the inner medullary collecting duct is highly permeable to water and urea; (4) fluid entering the inner medullary collecting duct contains relatively large amounts of urea; and (5) fluid entering the thin descending limb contains relatively large amounts of NaCl [10, 11].

In general, the water, NaCl, and urea permeabilities measured in loop of Henle and collecting duct segments by the study of isolated perfused tubule segments support the passive model. These permeability measurements are summarized in Table 1. As required by the model, the osmotic water permeability of thin descending limbs is extremely high [12–15]. In rabbit thin descending limb and hamster thin descending limb types I and III, sodium and urea permeabilities are low [9, 13–19], while in hamster thin descending limb type II, the sodium permeability is relatively high [14, 15]. Thus, it is evident that the rabbit data are entirely consistent with water absorption being the sole mechanism for concentrating the fluid in the thin descending limb. However, even in the hamster with the higher thin descending limb type II sodium permeability, the primary mechanism of solute concentration still is by water abstraction since the relative permeability of the thin descending limb to water is higher than to sodium.

In the thin ascending limb, osmotic water permeability is extremely low and NaCl permeability is high, consistent with the model [9, 12, 20, 21]. While this segment is not urea impermeable, the urea permeability is substantially less than the NaCl permeability [9, 12, 21], as required by the model.

The inner medullary collecting duct consists of two morphologically and functionally distinct subsegments [22–25]. The terminal inner medullary collecting duct is highly permeable to water and urea [24, 25] consistent with the model. However, the initial inner medullary collecting duct is highly permeable to water (in the presence of vasopressin) but not to urea [24, 25]. This pattern of urea permeabilities is advantageous for concentrating the urine maximally [26].

For a high urea concentration to exist in the fluid entering the terminal inner medullary collecting duct, very little urea must

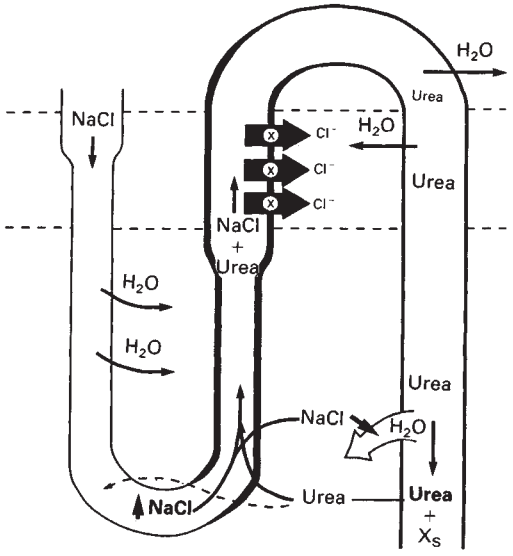

Fig. 1. *Schematic diagram of the passive equilibration model of the countercurrent multiplication system.* NaCl is actively absorbed from the thick ascending limb. In the presence of vasopressin, water is absorbed from the cortical, outer medullary, and initial inner medullary collecting duct while concentrating urea within the collecting duct lumen. This urea is absorbed from the terminal inner medullary collecting duct, generating a very high urea concentration within the deep inner medullary interstitium. The fluid which enters the thin ascending limb has a higher NaCl concentration and a lower urea concentration than the interstitium, resulting in passive NaCl absorption and dilution of the thin ascending limb [10, 11]. The NaCl concentration gradient across the thin ascending limb is higher than previously thought since the collecting duct absorbate has a low concentration of NaCl in juxtaposition to the thin ascending limb of Henle epithelium (Marsh, personal communication).

Table 1. Permeability properties of inner medullary nephron segments[a]

	Rabbit	Rat	Hamster
Thin descending limb type I			
Na × 10^{-5} cm/s	0.2 [16][b]		4.7 [15]
	1.6 [13][b]		
	1.9 [18][b]		
Urea × 10^{-5} cm/s	1.0 [19][b]	13 [9][b]	8.2 [15]
	1.5 [17][b]		
Osmotic water μm/s	2315 [13][b]	2139 [12][b]	1394 [15]
Thin descending limb type II			
Na	0.2 [16][b]		23 [14]
	1.6 [13][b]		66 [15]
	1.9 [18][b]		
Urea	1.0 [19][b]	13 [9][b]	2.3 [14]
	1.5 [17][b]		2.7 [15]
Osmotic water	2315 [13][b]	2139 [12][b]	2600 [15]
Thin descending limb type III			
Na			3.9 [14]
Urea			12.7 [14]
Osmotic water			1693 [14]
Thin ascending limb type IV			
Na	26 [20]	80 [12]	55 [21]
			88 [12]
Urea	6.7 [20]	23 [12]	19 [12]
		14 [9]	
Osmotic water	13 [20]	25 [12]	29 [12]
Initial inner medullary collecting duct			
Urea (−ADH)	1.2 [24]	3.4 [25]	
(+ADH)		4.1 [25]	
Osmotic water (−ADH)		15 [25]	
(+ADH)		148 [25]	
Terminal inner medullary collecting duct			
Na		1.1 [64]	
Urea (−ADH)	12 [24]	17 [25]	
(+ADH)		69 [25]	
Osmotic water (−ADH)		70 [25]	
(+ADH)		186 [25]	

[a] References are in parenthesis.
[b] Subsegment not specified, therefore cannot differentiate between thin descending limb type I and type II

be absorbed between the distal convoluted tubule and the initial inner medullary collecting duct. The urea permeability in all these nephron segments is quite low, even in the presence of vasopressin [24, 27–29]. As water is absorbed from these segments, urea is concentrated within the tubule lumen, resulting in delivery of a urea-rich fluid to the terminal inner medullary collecting duct. Thus, water, NaCl, and urea permeabilities of the various nephron segments fit the requirements of the passive mechanism.

Further support for the model comes from several in vivo studies. Fluid in the thin ascending limb has a lower osmolality than fluid in the thin descending limb at the same level of the inner medulla [6]. During antidiuresis, urea concentration is higher in the vasa recta than in the loops of Henle [5, 30], while NaCl concentration is lower in the vasa recta than in the loops of Henle [31, 32]. Finally, net NaCl absorption and net urea secretion have been demonstrated in vivo in hamster thin ascending limb [5]. Thus, there is substantial experimental data which support the passive mechanism.

Role of urea

The importance of urea to the generation of a concentrated urine has been appreciated since 1934, when Gamble et al described "an economy of water in renal function referable to urea" [33]. Subsequent micropuncture studies led to the concept of urea recycling: urea is absorbed from the inner medullary collecting duct [34] and secreted into the thin ascending limb [35], after which it remains within the tubule lumen until it returns to the inner medullary collecting duct. Maximal concentrating ability is decreased in protein-deprived animals and restored by urea infusion [30, 36, 37]. Thus, the passive mechanism, which critically depends on an adequate delivery of urea to the inner medulla, provides an explanation for the well described importance of urea to concentrating ability.

Several recent studies have improved our understanding of urea absorption across the inner medullary collecting duct. Sands and Knepper [24] demonstrated axial heterogeneity of urea permeability along the inner medullary collecting duct in both rat and rabbit, with a low urea permeability in initial inner medullary collecting ducts and a high urea permeability in terminal inner medullary collecting ducts (Table 1). Urea transport occurs by a vasopressin-stimulated facilitated transport process in terminal inner medullary collecting ducts [24, 25, 38, 39]. As the urea concentration in the lumen of terminal inner medullary collecting ducts exceeds that in vasa recta [30, 40–42], urea is rapidly absorbed into the inner medullary interstitium, down its concentration gradient. The low urea

permeability in initial inner medullary collecting ducts ensures that urea absorption is delayed until the deepest portion of the inner medulla, where it is needed to concentrate urine maximally [25, 26].

Prior to the demonstration of facilitated urea transport in terminal inner medullary collecting ducts, two mechanisms had been proposed to increase urea delivery to the inner medullary interstitium: (1) urea absorption across the papillary surface epithelium [43] and (2) urea absorption by solvent drag in the inner medullary collecting duct [26, 43–48]. In a recent study, the urea permeability of rabbit papillary surface epithelium was shown to be low [24], hence significant urea absorption across this epithelium does not occur. Several studies had measured a urea reflection coefficient of less than one, consistent with solvent drag [27, 49, 50]. In calculating the urea reflection coefficient, these studies did not include the effect of carrier-mediated urea transport, which tends to dissipate the imposed urea gradient. Recent studies which remeasured the urea reflection coefficient and included the measured dissipation of the imposed urea gradient in the calculation, concluded that the urea reflection coefficient is one [39, 51]. Phloretin inhibits urea transport, but not water transport, across terminal inner medullary collecting ducts, consistent with urea and water transport occurring by separate pathways [52, 53]. Thus, there does not appear to be evidence to support either significant recycling of urea across the papillary surface epithelium or solvent drag of urea.

Recent isolated perfused tubule studies modelled in vivo conditions by measuring fluid absorption from rat terminal inner medullary collecting ducts in the absence of an osmotic gradient but with a perfusate high in urea and a bath high in NaCl, and demonstrated significant fluid absorption [39]. Fluid absorption was due to generation of an osmotic gradient due to rapid urea absorption and not to solvent drag [39]. Thus, osmotic work can be performed across the terminal inner medullary collecting duct by high luminal urea concentrations and a high rate of urea transport. It remains to be tested by mathematical modelling whether the very high urea permeability of the terminal inner medullary collecting duct is sufficient to deliver enough urea to the inner medullary interstitium to drive the passive mechanism.

Within the inner medulla, collecting ducts and thin ascending limbs are virtually contiguous [54]. Some of the urea absorbed from terminal inner medullary collecting ducts will be secreted into thin ascending limbs (Fig. 1). This urea will remain in the tubule lumen until it returns to the terminal inner medullary collecting duct, completing a recycling pathway [55]. In addition, two other urea recycling pathways exist in the kidney [55]. One pathway is from terminal inner medullary collecting ducts to ascending vasa recta to thin descending limbs of short loop nephrons [56]. The other pathway is between cortical thick ascending limbs and proximal straight tubules [55]. Urea recycling serves to limit urea dissipation from the inner medulla [55].

Unresolved questions concerning the countercurrent system

Several mathematical modelling studies using idealized parameters have demonstrated that the passive mechanism can produce concentrated urine [11, 43, 57–59]. However, modelling studies using experimentally measured transport parameters have been unable to simulate the osmolality gradient known to exist in the medulla [26, 60]. This discrepancy could indicate that the passive model is insufficient to account fully for urinary concentration in the inner medulla, or that the mathematical models do not accurately reflect the true complexity present in the kidney. While it is beyond the scope of this review to examine the details of the various mathematical models, we wish to discuss the experimental data which appears to be inconsistent with the passive mechanism.

While the rabbit thin descending limb is relatively impermeable to NaCl and urea, recent permeability measurements from hamster thin descending limb type II found significant NaCl and urea permeabilities (Table 1). Solute fluxes across the thin descending limb would prevent generation of the NaCl and urea gradients necessary for passive dilution of the thin ascending limb. Micropuncture measurements of urea concentration at the bend of the loops of Henle (near the papillary tip) often exceed 280 mOsm/kg H_2O [5, 40]. Although this luminal urea concentration is less than in surrounding vasa recta, the difference is felt by some to be too small to drive the passive mechanism [5, 40, 61]. In addition, the thin ascending limb urea permeability is relatively high [9, 12, 20]. Urea entry into thin ascending limbs could dissipate the urea gradient within a short distance of the bend of the loop of Henle, eliminating the driving force for passive NaCl absorption. Furthermore, actual countercurrent exchange by the vasa recta is imperfect and thus dissipates part of the medullary gradients.

Although definitive answers to the problems posed by this data are not available, two recent hypotheses have been advanced, both of which incorporate an aspect of in vivo anatomic complexity which had been previously left out of models of the concentrating mechanism. Layton [62] has proposed a "distributed loop model" in which the simulated loops of Henle turn at multiple levels within the inner medulla. These simulations suggest that the passive mechanism needs to operate only near the bend of each loop of Henle, not along the entire length of each thin ascending limb [62]. As one ascends from the papillary tip towards the outer medulla, increasing numbers of loops turn, magnifying the effect of deeper loops [62]. Thus, the model of passive equilibration that has been modified by Layton is consistent with the in vivo data suggesting dissipation of the urea gradient in the thin ascending limb shortly after the loop bend. While it generates a greater osmotic gradient than models not including multiple lengths of long-loops, it does not reproduce in vivo osmotic gradients unless idealized transport parameters are chosen [62].

Marsh has recently included another aspect of inner medullary anatomy to this model. Lemley and Kriz have noted that inner medullary collecting ducts and thin ascending limbs are virtually contiguous [54]. Marsh has used this observation and has proposed that the actual gradient across the thin ascending limb is modelled more closely by absorbate from inner medullary collecting ducts than by vasa recta values (personal communication). Since the fluid absorbed from the inner medullary collecting duct is essentially free of NaCl, a steep concentration gradient is generated for passive NaCl absorption from the thin ascending limb. Using this approach, which he terms the "3-D Passive Countercurrent System", Marsh has been able to simulate in vivo osmotic gradients using measured transport parameters (personal communication). While other anatomic

details, such as inner medullary peristalsis [63] or vascular bundles [54] have yet to be modelled, these recent studies offer hope that the mystery of the concentrating mechanism within the inner medulla may soon be solved. We eagerly await the results of these and other mathematical modelling simulations.

Summary

Urinary concentration is achieved by countercurrent multiplication in the inner medulla. The single effect in the outer medulla is active NaCl absorption from the thick ascending limb. While the single effect in the inner medulla is not definitively established, the majority of experimental data favors passive NaCl absorption from the thin ascending limb. Continued experimental studies in inner medullary nephron segments will be needed to elucidate fully the process of urinary concentration.

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